

ASPECTS OF BIRTHS IN THE SHATBY HOSPITAL, ALEXANDRIA

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In 1963 and 1964 the Shatby Hospital was one of the 24 centres where the staff co-operated in a World Health Organization Study of Congenital Malformations (Stevenson, Johnston, Stewart, and Golding, 1966) and data additional to that collected in other centres were recorded, mainly in respect of complications of pregnancy. There are a number of unusual features of the Alexandria data which could not be dealt with in the above report and these are considered in this paper.

In all, 9,996 women were delivered after pregnancies lasting more than 27 weeks, there being 9,598 single births, 391 sets of twins, and seven sets of triplets. Data in respect of maternal toxæmia, hydramnios, and toxæmia were recorded for the last 8,553 of these pregnancies leading to single births and for 367 leading to twin births.

There were four features of particular interest in the Alexandria data relative to those from the other 23 centres in the WHO study:

(a) A very high frequency of malformations arising in structures developed from the neural tube; this was the second highest frequency in the study. The overall malformation frequency was low but not significantly lower than the average for the rest of the centres.

(b) A very high frequency of twinning, the highest in any centre, which as might be expected, was accounted for almost entirely by dizygotic twins.

(c) A high overall mortality in terms of stillbirths and children who died before leaving hospital.

(d) A remarkably high consanguinity rate in the marriages of the mothers.

NEURAL TUBE DEFECTS

The frequencies in single births of neural tube defects and those from all other centres are set out in Table I. It will be seen that the figures for all groups of neural tube defects are considerably higher for Alexandria than those for the other centres combined. Only Belfast, Northern Ireland, had a higher overall neural tube defect frequency and this was mainly due to anencephalus.

TWINNING DATA

Of 9,996 deliveries in Alexandria, 391 (3.9 per cent.) resulted in twin pairs. Of these 116 were male/male, 114 female/female, and 161 male/female. The mean twinning rate in all centres was 1.24 per cent. and the next highest rate to that in Alexandria was only 1.9 per cent. The estimated monozygous (MZ) frequency in Alexandria was 0.69 per cent. and of dizygous (DZ) pairs 3.21 per cent. These may be compared with mean frequencies in the 24 centres of 0.44 and 0.81 per cent. respectively.

An interesting finding was that over all the centres there was a correlation of 0.651 ($P < 0.001$) between the mean neural tube frequencies and

TABLE I

SINGLE BIRTHS—FREQUENCIES PER 1,000 LIVE AND STILL BIRTHS (STANDARDIZED FOR MATERNAL AGE) OF NEURAL TUBE DEFECTS IN THE SHATBY HOSPITAL AND THOSE IN ALL CENTRES IN THE WHO STUDY

Centre	Anencephalus	Anencephalus + Spina bifida	Hydrocephalus Alone	Hydrocephalus + Spina bifida	Occipital Meningocele	Spina bifida Alone	Other Neural Tube Defects	Total Neural Tube Defects
Alexandria	3.18 (30)	0.61 (6)	1.99 (20)	0.58 (6)	0.24 (2)	0.83 (8)	0.45 (4)	7.88 (76)
All Centres	0.92	0.13	0.61	0.26	0.04	0.55	0.08	2.59

N.B.—The numbers in brackets under the Alexandria frequencies are the numbers of cases.

estimated dizygous twinning frequencies. Of the 204 pregnancies resulting in like-sexed twins where toxæmia was recorded, in 24 (11·8 per cent.) the mothers had toxæmia. Of the mothers of the 143 unlike-sexed twin pairs, 21 (14·7 per cent.) had toxæmia. This leads to an estimated frequency of toxæmia with MZ pairs of 4·9 per cent. and in DZ pairs of 14·7 per cent. This difference is significant at a 1 per cent. level.

These findings in respect of twinning and toxæmia are in the same direction as those from Belfast, where in 545 twin pregnancies the estimated frequency of toxæmia with MZ and DZ pairs was respectively 4·7 and 25·5 per cent. in hospital births. This difference is also significant at a 1 per cent. level. Such differences are relevant to any incompatibility hypothesis of pre-eclamptic toxæmia. The frequency of consanguinity in the parents of twins does not differ significantly from the frequency in parents of singletons. There was no difference in consanguinity frequency in parents of like and those of unlike-sexed twins.

MORTALITY

The stillbirth rate in Alexandria was the highest in any of the 24 co-operating centres, being 82 per 1,000 total births. The average for the remaining centres was 24·2 per 1,000. The relationship of these losses to consanguinity is considered below.

CONSANGUINITY

Of 9,586 single births in Alexandria where the presence or absence of consanguinity was recorded, the parents were related in 3,155 (32·9 per cent.). The first-cousin marriage rate was 22·0 per cent. and that of lesser degrees of relationship was 10·9 per cent., and there is some reason for believing that the lesser degrees of relationship were under-reported. How-

ever, ascertainment of first-cousin relationships is likely to be rather accurate, as the four possible types of first cousins are each described differently in Arabic and are well understood by the mothers questioned. These are very high consanguinity rates, being three times as high as in any other centre. The frequency of consanguinity was not related to parity or maternal age. It is important to examine the frequencies of malformations and of "perinatal" deaths in the offspring of related and unrelated parents.

Consanguinity, Stillbirths, and Early Deaths of Infants.—The associations of consanguinity in different degrees with stillbirths and deaths of infants in the maternity hospital before discharge are shown in Table II. These early infant deaths are approximately but not exactly the same as first-week deaths. There is no reason to suppose that infants born of consanguineous and non-consanguineous marriages stay in hospital for different lengths of time.

It will be seen that there is a significant increase in the frequency of stillbirths in the offspring of related parents mainly contributed by first-cousin marriages and that the numbers of hospital deaths are small. However, analysis of these stillbirths shows an overwhelming contribution from deaths from neural tube defects which, as will be shown below, are associated with parental consanguinity. Considering only stillbirths and early deaths in children who were not malformed, as will be seen from Table II, the influence of consanguinity disappears. However, the data in the last column of the Table show that in the other centres in the WHO study there is a consistent effect of inbreeding on mortality even when malformed children are excluded in the data. (The differences between

TABLE II

STILL BIRTHS AND EARLY INFANT DEATHS—SINGLE BIRTHS AND CONSANGUINITY OF PARENTS

Relationships of Parents	Still Births Alexandria		Infant Deaths Early in Hospital Alexandria		Still Births and Early Deaths in Hospital			
	Number	Frequency per 1,000 Total Births	Number	Frequency per 1,000 Live Births	Number	Frequency per 1,000 Total Births		
						All Births Alexandria	Excluding Malformed Births	
					Alexandria	All Other Centres in WHO Study		
First Cousins Related but Less Closely than First Cousins	203	96·21	13	6·82	216	102·37	86·87	65·96
	76	72·66	6	6·19	82	78·39	70·53	49·83
All Related ..	279	88·40	19	6·60	298	94·42	81·42	62·10
Not Related ..	506	78·69	49	8·27	555	86·31	80·70	35·93

mortality in offspring of first cousins and those related in lesser degree is significant at a 0.1 per cent. level, as is the difference between the mortality of the offspring of these related in lesser degree and of those not related.)

The explanation of the Alexandria data probably lies in the high frequency of lesser degrees of consanguinity not identified and in the high, presumably mainly socio-economically determined, perinatal wastage. Such deaths must so outnumber those due to consanguinity effects *per se* that they mask its manifestations.

Consanguinity and Malformations.—In all 111 malformed children were born in the 9,598 single births, a frequency of 11.6 per 1,000 total births. These are major malformations of types fully specified in the WHO report. They do not include hypospadias, hydrocoele, undescended testicles, hernias, minor ear malformations, naevi, moles, etc. The conditions from which the children suffered and the relationships of their parents are shown in Table III.

TABLE III
CONSANGUINITY AND MALFORMATIONS
ALEXANDRIA

Malformation	No. of Cases	Cases with Parental Consanguinity					
		No.			Per cent.		
		FC	LFC	T	FC	LFC	T
Anencephalus with and without Spina bifida	36	14	11	19	38.9	13.9	52.8
Hydrocephalus only	20	7	2	9	35.0	10.0	45.0
Hydrocephalus + Spina bifida	6	4	0	4	66.7	0	66.7
Other Neural Tube Defects	6	1	1	2	16.7	16.7	33.3
Spina bifida	8	4	1	5	50.0	12.5	62.5
Congenital Heart Disease	1	0	1	1	0	100.0	100.0
Malformations of Gut	4	0	0	0	0	0	0
Harelip with or without associated Cleft Palate	9	2	0	2	22.2	0	22.2
Talipes	5	0	0	0	0	0	0
Malformations of Extremities	5	1	0	1	20.0	0	20.0
Other Skeletal Malformations	2	1	0	1	50.0	0	50.0
Miscellaneous	4	1	1	2	25.0	25.0	50.0
Multiple Defects	5	2	0	2	40.0	0	40.0
Total	111	37	11	48	33.3	9.9	43.2

SUMMARY

All Neural Tube Defects	76	29	9	38	38.2	11.8	50.0
All Other Defects	35	8	2	10	22.8	5.7	28.5
All Not Malformed	9,475	2,072	1,035	3,107	21.9	10.9	32.8

It will be seen, however, that the entire contribution to association of consanguinity with malformations is from the neural tube defects and that half

of this is due to anencephalus. The frequency of parental consanguinity in children with all neural tube defects (38/76) is significantly greater than in non-malformed children (3,107/9,475): $\chi^2=29.40$; d.f.=1; $P<0.001$. This association was not demonstrated before the WHO Study, but in that investigation the association was also found in the data from Bombay.

Consanguinity and Disturbances of Pregnancy.—

As already noted the presence or absence of hydramnios, toxæmia of pregnancy, and maternal diabetes was recorded in 8,553 pregnancies which resulted in single births. The inter-relationships of these maternal conditions, consanguinity, and survival or malformation of the infants are indicated in Table IV (opposite).

In the sample of 8,553 single births, the frequency of first-cousin marriages was 22.1 per cent. and of relationships of lesser degree 11.2 per cent. The comparable figures for all the 9,586 single births where consanguinity was recorded were 22.0 per cent. and 10.9 per cent. It would seem then that, in respect of consanguinity, these 8,553 were reasonably representative of the whole.

Consanguinity and Hydramnios.—In view of the high frequencies of neural tube defects in Alexandria and the well-known relationship with hydramnios it might have been expected that the frequency of hydramnios would be high. It is notoriously difficult to get agreed criteria or to apply them to the diagnosis of hydramnios. In Alexandria 51 (0.6 per cent.) of all mothers were recorded as having this complication of pregnancy. The difficulties of diagnostic comparability make it virtually impossible to draw any conclusions. Of these 51 mothers, eleven also had toxæmia, one had diabetes, and two had toxæmia and diabetes (Table IV, opposite). Eighteen (35.3 per cent.) were related to their husbands and twelve of the 37 mothers (32.4 per cent.) who had hydramnios only were related. Neither proportion differs significantly from that of consanguinity of all parents and the figures do not suggest any lesser consanguinity frequency in women with hydramnios who are related to their husbands—which might have been expected if hydramnios represented a maternal/foetal incompatibility.

The frequency of malformations in the offspring of women with hydramnios was 16/51 (31.4 per cent.) and most of the malformations were of the neural tube type. As will also be noted the mortality of foetuses was very high.

Consanguinity and Diabetes.—38 of the mothers of single-born children had diabetes. Of these

TABLE IV

SINGLE BIRTHS—DISTURBANCES OF PREGNANCY—"PERINATAL" DEATHS—MALFORMATIONS AND CONSANGUINITY

Disturbances of Pregnancy	Number of Births			Per cent. of All Single Births	Major Malformations of Child				Survival of Infants				Still-birth Rate per 1,000 Total Births	Deaths in Hospital per 1,000 live Births	Consanguinity				
	Male	Female	Total		Y	N	Total	Per cent. Y	LBA	LBD	SB	Total			None	First Cousins	Less than First Cousins	All Consanguinity	Per cent. of Consanguineous parents
Toxaemia (only) ..	379	318	699*	8.71	8	691	699	1.14	477	9	213	699	305	18.5	491	143	65	208	29.76
Hydramnios (only) ..	15	22	37	0.43	11	26	37	29.72	21	1	15	37	405	45.4	25	10	2	12	32.43
Toxaemia and Hydramnios ..	4	7	11	0.13	5	6	11	45.45	4	—	7	11	636	—	5	5	1	6	54.55
Diabetes (only) ..	13	14	27	0.32	1	26	27	3.70	17	—	10	27	370	—	19	7	1	8	29.63
Diabetes and Hydramnios ..	0	1	1	0.01	0	1	1	—	0	—	1	1	—	—	1	0	0	0	—
Diabetes and Toxaemia	3	5	8	0.09	1	7	8	12.50	3	—	5	8	625	—	6	0	2	2	25.00
Toxaemia, Hydramnios, and Diabetes ..	1	1	2	0.02	0	2	2	—	1	—	1	2	500	—	2	0	0	0	—
None of the Above ..	4,081	3,684	7,768*	90.82	62	7,706	7,768	0.80	7,292	43	433	7,768	56	5.81	5,157	1,728	883	2,611	33.61
TOTAL	4,496	4,052	8,553	100.00	88	8,465	8,553	1.03	7,815	53	685	8,553	80	6.71	5,706	1,893	954	2,847	33.29

*Total of males and females less than "T" because of children whose sex was not determinable.

one also had hydramnios, eight also had toxaemia, and two had both toxaemia and hydramnios. Of these mothers ten (26.3 per cent.) were related to their husbands. The consanguinity frequency does not differ significantly from that in all mothers of single-born children who had no recorded upset of pregnancy.

Consanguinity and Toxaemia.—Pre-eclamptic toxaemia was recorded when women had blood pressures of 130/90 mm. Hg on at least two occasions after the 20th week of pregnancy and had, in addition, oedema, albuminuria, or raised blood urea levels. As mothers seldom attended before 20 weeks, essential hypertension could seldom be excluded, but those cases could not have contributed more than 10 per cent. to the total and the proportion, in the absence of any evidence, may be assumed to be approximately the same in women who were or were not related to their husbands.

In 5,706 marriages of unrelated persons, 491 (8.6 per cent.) mothers had toxaemia of pregnancy (excluding five mothers who also had hydramnios and toxaemia). In 2,847 consanguineous marriages, 208 mothers (7.3 per cent.) had toxaemia. The smaller frequency in mothers related to their husbands is significant at a 5 per cent. level. The consanguinity coding used in Alexandria was simple—none known, first cousins, and lesser degrees of relationship; the frequency of toxaemia in mothers whose husbands were first cousins was 143/1,893 (7.5 per cent.) and in those related to their husbands in lesser degrees it was 65/954 (6.8 per cent.).

The finding for all consanguinity is of interest but it might have been expected that there would be less

toxaemia when the woman's husband was her first cousin than when the relationship was less close, whereas there was rather more in first cousins although the difference is not significant $\chi^2=0.38$; $P<0.5$. An unusual feature of the toxaemia data in Alexandria is that, as may be seen from Table V, toxaemia does not occur more commonly in first births as is the usual finding. Toxaemia in "grand-multipara" is the main contributor to the findings.

TABLE V
PREGNANCY ORDER AND TOXAEMIA

Pregnancy Order	Numbers of Mothers with Toxaemia		χ^2
	Observed	Expected	
1	65	67.0	0.03
2	75	83.3	0.73
3	46	72.3	9.21*
4	45	58.7	2.97
5	40	56.7	4.63*
6	43	45.6	0.10
7	49	41.7	1.11
8+	186	123.8	30.75*
Total	699	699	49.53 (d.f. = 7; $P<0.001$)

* Significant at 1 per cent. level.

In view of the interest of the findings, another prospective study has now been started. In this there will be more detailed definition of consanguinity in spouses, collection of similar data concerning consanguinity in parents of the mothers of the patient, more precise recording of the basis of diagnosis of pre-eclampsia, and examination of possible biases associated with socio-economic status, admission to hospital for confinement, etc.

DISCUSSION

It seems clear that in Alexandria some of the aspects of maternal health, survival of the foetus, and consanguinity of parents are very unusual, if not unique, and seem to merit further *ad hoc* study. The association of parental consanguinity and neural tube defects was unexpected. Part of this relationship could be a reflection of the frequency of neural tube defects in mothers in the lowest socio-economic group if more of such mothers marry relatives than those who are less poor. The association of high frequency of neural tube defects with poor socio-economic conditions has been demonstrated on numerous occasions from national vital statistics. The high dizygous twinning frequency in Alexandria

also offers an opportunity for testing for any associations with socio-economic variations.

The data on consanguinity and of twin pregnancies and toxæmia are of particular interest and appear to merit further study.

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